Clinical trial results:
A DOUBLE-BLIND, PLACEBO-CONTROLLED, STUDY TO EVALUATE THE EFFICACY AND SAFETY OF 24 WEEKS TREATMENT WITH REN001 IN PATIENTS WITH PRIMARY MITOCHONDRIAL MYOPATHY (PMM)

Summary

EudraCT number	2020-002855-40
Trial protocol	FR CZ DK HU BE IT ES NL NO
Global end of trial date	05 October 2023

Results information

Result version number	v1 (current)
This version publication date	15 December 2024
First version publication date	15 December 2024

Trial information

Trial identification

Sponsor protocol code	REN001-201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04535609
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Reneo Pharma Ltd.
Sponsor organisation address	6707 Winchester Circle Suite 400, Boulder, United States, 80301
Public contact	Ann Howell, OnKure Inc, 01 720-307-2892, ahowell@onkure.com
Scientific contact	Ann Howell, OnKure Inc, 01 720-307-2892, ahowell@onkure.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 January 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 September 2023
Global end of trial reached?	Yes
Global end of trial date	05 October 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of REN001 in subjects with PMM treated for 24 weeks, assessed by the effect on exercise endurance.

Protection of trial subjects:

Review of blinded subject safety data (including adverse events [AEs], electrocardiograms, laboratory safety tests, vital signs, and physical and ophthalmologic examinations) was performed by the Reneo Safety Review Committee (SRC) in accordance with the REN001-201 SRC Charter. Safety reviews were conducted throughout the study in order to identify any potential safety signals during the trial that may have impacted the safety of the participants. The SRC couldmake recommendations concerning continuation, termination or other study modifications based on these reviews.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 April 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 21
Country: Number of subjects enrolled	Spain: 18
Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	Czechia: 11
Country: Number of subjects enrolled	France: 22
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Hungary: 7
Country: Number of subjects enrolled	Italy: 41
Country: Number of subjects enrolled	Australia: 12
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	New Zealand: 5
Country: Number of subjects enrolled	United Kingdom: 19
Country: Number of subjects enrolled	United States: 24
Country: Number of subjects enrolled	Norway: 2
Country: Number of subjects enrolled	Denmark: 3
Worldwide total number of subjects	212
EEA total number of subjects	144

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	196
From 65 to 84 years	16
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment was done from across 41 centers worldwide.

Pre-assignment

Screening details:

One subject completed all screening procedures, was randomized in error (to placebo treatment) and was removed from the study before any study procedures were completed. This subject is not included in the reporting groups.

Period 1

Period 1 title	Treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Blinding implementation details:

REN001 and placebo was provided as visually matched capsules. All study drug was supplied in identical bottles thereby maintaining the double blind conditions for the participant and investigator.

Arms

Are arms mutually exclusive?	Yes
Arm title	REN001

Arm description:

100 mg REN001 as 2 x 50 mg capsules administered once daily with food for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	REN001
Investigational medicinal product code	
Other name	Mavodelpar, HPP593
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

100 mg REN001 capsules as 2 x 50 mg once daily with food for 24 weeks.

Arm title	Placebo

Arm description:

2 placebo capsules administered once daily with food for 24 weeks.

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

2 placebo capsules administered once daily with food for 24 weeks.

Number of subjects in period 1	REN001	Placebo
Started	108	104
Week 24	100	98
Completed	99	97
Not completed	9	7
Adverse event, serious fatal	1	-
Consent withdrawn by subject	3	1
Adverse event, non-fatal	2	3
Wish to become pregnant	-	1
Lost to follow-up	1	2
Protocol deviation	2	-

Baseline characteristics

Reporting groups	
Reporting group title	REN001
Reporting group description:	
100 mg REN001 as 2 x 50 mg capsules administered once daily with food for 24 weeks.	
Reporting group title	Placebo
Reporting group description:	
2 placebo capsules administered once daily with food for 24 weeks.	

Reporting group values	REN001	Placebo	Total
Number of subjects	108	104	212
Age categorical			
Units: Subjects			
Adults (18-64 years)	97	99	196
Adults (>=65 years)	11	5	16
Age continuous			
Units: years			
arithmetic mean	46.8	46.3	
standard deviation	± 13.69	± 11.93	-
Gender categorical			
Gender Categorical, Male or Female			
Units: Subjects			
Female	75	76	151
Male	33	28	61

End points

End points reporting groups

Reporting group title	REN001
Reporting group description:	
100 mg REN001 as 2 x 50 mg capsules administered once daily with food for 24 weeks.	
Reporting group title	Placebo
Reporting group description:	
2 placebo capsules administered once daily with food for 24 weeks.	

Primary: Change in distance walked during 12 minute walk test

End point title	Change in distance walked during 12 minute walk test
End point description:	
Change from baseline at Week 24 in distance walked during the 12-minute walk test (12MWT). The analysis was based on the full analysis set (FAS) including subjects in the randomized set who received at least one dose of study drug and were not subsequently discontinued from the study for failing eligibility criteria.	
End point type	Primary
End point timeframe:	
24 weeks	

End point values	REN001	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106[1]	104[2]		
Units: meters				
arithmetic mean (confidence interval 95%)	26.75 (12.97 to 40.53)	30.89 (15.03 to 46.74)		

Notes:

[1] - Subjects in the FAS with data at Week 24 (N=2 missing, N=2 withdrawn). N=102 analysed.

[2] - Subjects in the FAS with data at Week 24 (N=4 missing, N=2 withdrawn). N=98 analysed.

Statistical analyses

Statistical analysis title	Estimated difference between treatment groups
Statistical analysis description:	
REN-001 minus placebo for the change from baseline. Missing values were imputed.	
Comparison groups	REN001 v Placebo
Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	equivalence[3]
P-value	= 0.8962
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.59

Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.24
upper limit	25.42
Variability estimate	Standard error of the mean
Dispersion value	12.158

Notes:

[3] - The changes from baseline in distance walked during the 12MWT for the FAS were analyzed using a mixed effect model for repeated measures (MMRM). The model included fixed terms for treatment, visit and the treatment-by-visit interaction. The model also included the stratification mutation factor and continuous baseline distance walked during the 12MWT as covariates. Missing values were imputed prior to analysis using multiple imputation or imputations for intercurrent events.

Secondary: Change in PROMIS Short Form - fatigue 13a (FACIT-fatigue) scores

End point title	Change in PROMIS Short Form - fatigue 13a (FACIT-fatigue) scores

End point description:

Change from baseline at Week 24 in PROMIS® Short Form – Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue 13a T-score. The analysis was based on the FAS including subjects in the randomized set who received at least one dose of study drug and were not subsequently discontinued from the study for failing eligibility criteria.

End point type	Secondary

End point timeframe:

24 weeks

End point values	REN001	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106[4]	104[5]		
Units: score on a scale				
arithmetic mean (confidence interval 95%)	-0.98 (-2.03 to 0.08)	-2.60 (-3.80 to -1.40)		

Notes:

[4] - Subjects in the FAS with data at Week 24 (N=3 missing, N=2 withdrawn). N=101 analysed.

[5] - Subjects in the FAS with data at Week 24 (N=3 missing, N=2 withdrawn). N=99 analysed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Day 1 until follow-up visit 21 to 28 days after the last study dose

Adverse event reporting additional description:

The incidence, causality and severity of treatment-emergent AEs, including treatment-emergent serious AEs and AEs of special interest was documented.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	REN001
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	REN001	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 108 (7.41%)	7 / 104 (6.73%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	1 / 108 (0.93%)	0 / 104 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 108 (0.93%)	0 / 104 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical vertebral fracture			
subjects affected / exposed	0 / 108 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury			

subjects affected / exposed	0 / 108 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 108 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 108 (0.93%)	0 / 104 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	0 / 108 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 108 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nodal rhythm			
subjects affected / exposed	0 / 108 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Hospitalisation			
subjects affected / exposed	1 / 108 (0.93%)	0 / 104 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cranial operation			
subjects affected / exposed	0 / 108 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Cerebrovascular accident			
subjects affected / exposed	2 / 108 (1.85%)	0 / 104 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 108 (0.93%)	0 / 104 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 108 (0.93%)	0 / 104 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 108 (0.93%)	0 / 104 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Gastrointestinal disorders			
Haematemesis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 108 (0.93%)	0 / 104 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 108 (0.93%)	0 / 104 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			

subjects affected / exposed	1 / 108 (0.93%)	0 / 104 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	0 / 108 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia influenzal			
subjects affected / exposed	0 / 108 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	1 / 108 (0.93%)	0 / 104 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	REN001	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	85 / 108 (78.70%)	81 / 104 (77.88%)	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	11 / 108 (10.19%)	3 / 104 (2.88%)	
occurrences (all)	11	3	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	6 / 108 (5.56%)	1 / 104 (0.96%)	
occurrences (all)	9	1	
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 108 (9.26%)	13 / 104 (12.50%)	
occurrences (all)	13	21	
Dizziness			

subjects affected / exposed	7 / 108 (6.48%)	3 / 104 (2.88%)	
occurrences (all)	7	3	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	7 / 108 (6.48%)	9 / 104 (8.65%)	
occurrences (all)	7	10	
Eye disorders			
Refraction disorder			
subjects affected / exposed	20 / 108 (18.52%)	15 / 104 (14.42%)	
occurrences (all)	28	18	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	10 / 108 (9.26%)	3 / 104 (2.88%)	
occurrences (all)	10	3	
Nausea			
subjects affected / exposed	10 / 108 (9.26%)	4 / 104 (3.85%)	
occurrences (all)	10	4	
Vomiting			
subjects affected / exposed	7 / 108 (6.48%)	5 / 104 (4.81%)	
occurrences (all)	8	5	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	8 / 108 (7.41%)	0 / 104 (0.00%)	
occurrences (all)	10	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	9 / 108 (8.33%)	4 / 104 (3.85%)	
occurrences (all)	9	5	
Myalgia			
subjects affected / exposed	9 / 108 (8.33%)	6 / 104 (5.77%)	
occurrences (all)	15	9	
Arthralgia			
subjects affected / exposed	2 / 108 (1.85%)	6 / 104 (5.77%)	
occurrences (all)	2	7	
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	5 / 108 (4.63%)	11 / 104 (10.58%)	
occurrences (all)	5	9	
COVID-19			
subjects affected / exposed	20 / 108 (18.52%)	13 / 104 (12.50%)	
occurrences (all)	21	13	
Metabolism and nutrition disorders			
Vitamin D deficiency			
subjects affected / exposed	6 / 108 (5.56%)	3 / 104 (2.88%)	
occurrences (all)	6	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 June 2022	- removed the requirement for at least 40% of subjects in study REN001-201 to have the m.3243A>G genotype - update on eye examination to delete redundant text and clarify lens grading and visual acuity - update on statistical methods: primary analysis updated to MMRM; update of analysis model secondary endpoint (MFIS physical subscale) - clarified that re-screened subjects are not required to repeat their Screening eye examinations or Dual-energy X-ray absorptiometery scans within 6 months of the original assessments - reflected that the REN001 open-label extension study is available, for subjects who complete REN001-201, in countries where the extension study is approved - clarified that study centers can complete the Baseline, Week 12, Week 24 and Early Termination visits over two days at the Investigator's discretion - clarified the postmenopausal definition for consistency with the central lab to women of 45 years and older and amenorrhoeic for 1 year in addition to an FSH level indicating postmenopausal state - Belgium ethics committee requested that the reason for ethnicity being collected (regarding estimated Glomerular Filtration Rate calculation) is mentioned in the protocol - was added

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported